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Research Article

Elevated uric acid levels: a predictor of pulmonary hypertension

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ABSTRACT

Background: Pulmonary hypertension is a chronic, progressive and a fatal disease. Uric Acid is elevated in case of myelo and lymphoproliferative diseases, decreases uric acid excretion or as a part of metabolic syndrome (insulin resistance). It is also said to be associated in patients with heart failure leading to severe symptoms and fatality. This study was conducted to identify if elevated uric acid levels can be a predictor of pulmonary hypertension.
Methods: After taking the detailed demographic data of 62 patients, a thorough clinical and physical examination, postero-anterior chest X-rays, pulmonary function testing, ventilation or perfusion scintigraphy and Electro Cardiograph was also done for all the patients. Blood was drawn for testing uric acid, creatinine and total bilirubin levels.
Results: Out of the 62 patients, 43.5% were males and 56.5% were females. Out of the NYHA classes, most of the patients 58% belonged to the Class II, 34% to class III and 8% to Class IV. . The total bilirubin and creatinine levels were higher in patients with hyperuricemia than that of the controls. The blood saturation levels were significantly lower with only 67% and heart rate was on average more than 89 beats per minute. A positive correlation with NYHA class and MPAP, and a negative correlation with LVEF and RVEF were observed.
Conclusions: In conclusion, the results of this study establish that hyperuricemia is common in patients with severe PH.

Keywords: Elevated uric acid, Pulmonary hypertension, Predictor, Pulmonary arterial pressure

INTRODUCTION

Pulmonary hypertension is defined by a mean pulmonary artery pressure of at least 25 mmHg at rest or 30 mmHg with exertion based on right heart catheterization. It is a chronic, progressive and a fatal disease. It is usually characterized by increase of pulmonary vascular cells and reduction of small pulmonary arteries, leading to increased pulmonary vascular resistance and eventually right heart failure and death. PAH is seen in any age-from infancy to elderly. In the last decade, new pharmacological therapies have been developed that improve hemodynamics, exercise capacity, and survival in this patients.[1]

Serum uric acid is the end product of purine degradation with the normal ranges at 2.4-6.0 mm Hg. It is elevated in case of myelo and lymphoproliferative diseases, decreases uric acid excretion or as a part of metabolic syndrome (insulin resistance).[2] It is also said to be associated in patients with heart failure leading to severe symptoms and fatality.[3] It is also associated with cyanotic congenital heart disease and obstructive pulmonary disease.[4-7]

Primary pulmonary hypertension (PPH) ultimately produces right ventricular failure which is associated with markedly reduced cardiac output and mild hypoxia.[8-10] There have been few studies which have reported that patients with severe PPH have elevated uric acid levels. Thus, this study was conducted to identify if elevated uric acid levels can be a predictor of pulmonary hypertension.

METHODS

62 patients who were referred to the pulmonology department in Mediciti Institute of Medical Sciences, during the period of two years, and diagnosed with pulmonary hypertension (i.e. mean pulmonary arterial pressure >22 mmHg) were included into the study.

After taking the detailed demographic data of the patients, a thorough clinical and physical examination was taken for all the patients. Postero-anterior chest X-rays, pulmonary function testing, ventilation or perfusion scintigraphy and Electro Cardiograph was also done for all the patients. 50 healthy subjects were also recruited into the study for the evaluation of uric acid levels.

Patients with diabetes mellitus, renal dysfunction, hepatic diseases, thromboembolic disease, obstructive pulmonary disease, interstitial lung diseases, and congenital cardiac abnormalities had been excluded.

Clinical profile of the patients included categorization of New York Heart Association (NYHA) Class, oxygen saturation, measurement of pulmonary arterial pressure, pulmonary vascular resistance, and cardiac output.

Standard parasternal long-axis, short-axis, and apical four- and two-chamber views were obtained, and the right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) were calculated using a modified Simpson's formula.

Blood for all the patients were collected as per the regular protocols, with 5 ml of blood being collected from anticubital vein by sterile methods in a plain tube without any anticoagulants. The blood was allowed to clot for 30 minutes at room temperature and then was centrifuged at 1000rpm for 10 minutes to obtain the sera.

The sera were then used for evaluation of blood glucose, uric acid, creatinine, Total cholesterol, HDL cholesterol and triglycerides.

Statistical analysis was performed using SPSS version 13.0. The data was expressed as mean±SD. Comparisons were done using one way ANOVA, Fisher's tests and Pearson's coefficient. $P<0.05$ was taken as significant value.

RESULTS

Out of the 62 patients, 27 (43.5%) were males and 35 (56.5%) were females. Out of the NYHA classes, most of the patients (36 no) belonged to the class II (58%), 21 (34%) to class III and 5 (8%) to class IV (Figure 1).

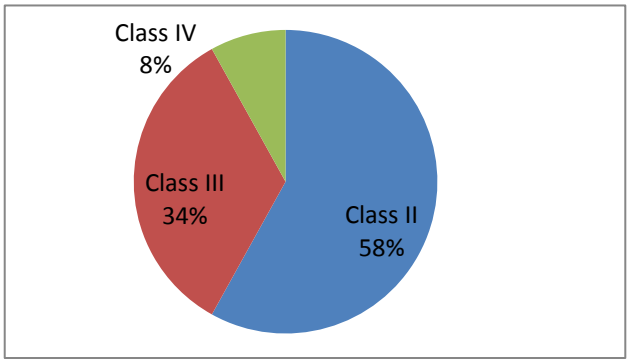

Figure 1: Categorization of NYHA class.

The age of the patients was slightly higher than those of the controls. The levels of uric acid among the patients were significantly higher than that of the controls with the mean value being 7.1 mg/dl. The total bilirubin and creatinine levels were also higher than that of the controls. The blood saturation levels was significantly lower with only 67% and heart rate was on average more than 89 beats per minute (Table 1).

Table 1: Comparison of patient and control characteristics.

Characteristics	Patients (62)	Controls (50)
Age	44.2 ± 10.2	36.1±6.5
Sex (M/F)	27/35	21/29
Uric acid mg/dl	7.1 ± 2.6	4.7 ± 2.9*
Creatinine mg/dl	1.9 ± 0.5	0.8 ± 0.6*
Total bilirubin (mg/dl)	1.7 ± 0.9	0.9 ± 0.1*
Blood O_2 saturation %	67 ± 14	88± 9*
Heart rate	89 ±6	75 ± 7*
Spap mmHg	19.8 ± 2.1	13.5 ± 2.3*
Dpap mmHg	11.4 ± 1.8	8.4 ± 1.7*
MPAP MmHg	16.1± 1.4	11.4 ± 0.5*
Cardial Output L/min	2.4 ± 0.8	3.8 ± 0.6*
Left ventricular ejection fraction%	41.8 ± 4.1	44.6 ± 3.7
Right ventricular ejection fraction %	40.6 ± 4.1	48.3 ± 4.3

*P value <0.01 significant

The correlation between the uric acid and variables such as Left ventricular function, right ventricular function, mean pulmonary arterial pressure, and NYHA class was done by Pearsons's correlation analysis. All the values showed significant correlation (Table: 2).

Table 2: Correlation between uric acid and MPAP, LVEF, RVEF and NYHA class.

Variables	Correlation coefficient	P value
MPAP	0.401	<0.01
LVEF	-0.538	<0.01
RVEF	-0.476	<0.01
NYHA Class	0.44	<0.01

Of the total 62 patients, 8 patients died during the hospital stay or during the 1 year follow up. Of them, the majority of them (5 in no) had a uric acid level of >8 mg/dl, 2 had between 6.1-8.0 mg/Hg and 1 had a uric acid level of less than 6 mmHg (Figure 2).

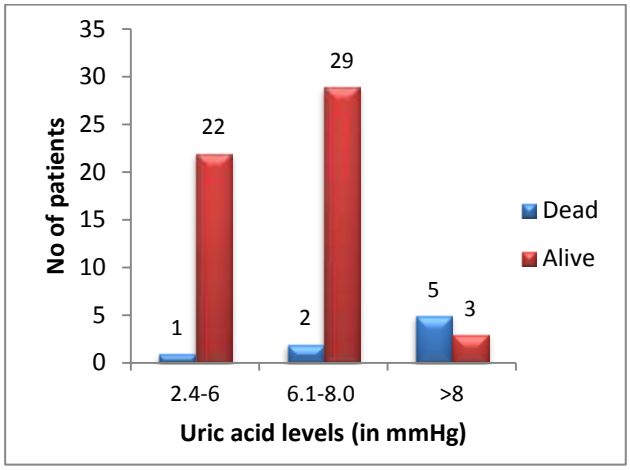

Figure 2: relationship between uric acid levels and mortality.

DISCUSSION

Pulmonary arterial hypertension is a severe progressive disease characterized by vasoconstriction, vessel wall remodeling and platelet aggregation. Elevated pulmonary vascular resistance and low cardiac output are strongly correlated to mortality, so that monitoring of pulmonary arterial pressure requires repeated invasive procedures such as right heart catheterization for assessing the benefit of the treatment or the need for transplantation.[11,12]

In our study, we found the levels of uric acids higher in the patients with pulmonary hypertension than in healthy subjects. This was accordance to a similar study by Zhang et al, where in the uric acid levels were elevated.[13] They found a positive correlation between uric acid levels and the MPAP.

Hemodynamic parameters, including right atrial pressure, pulmonary arterial pressure, pulmonary vascular resistance, and cardiac index, are considered indicators for the severity of disease in PAH and are associated with prognosis.[14-16] Voelkel et al found elevated serum uric acid levels in patients with Primary PH especially those with elevated mean RAP. Since an elevated RAP is a reflection of right heart failure, they found it to be possible that the elevation of serum UA was related to right heart failure.[17]

There was negative correlation between uric aacid and LVEF and RVEF, while it was positive correlation with MPAP and NYHA class. The serum creatinine levels and total bilirubin levels were also high. So was the systolic and diastolic PAP, while the heart rate and the cardiac output were significantly lower. There was no statistical significance in the age of the patients and sex of the patients although a greater number of them were women.

The actual reason for the increase in uric acid in patients with pulmonary hypertension remains unclear. It is assumed that one of the contributors can be lung tissue ischemia. Earlier studies have shown that the production of uric acid is increases in proportion to severity of hypoxia in patients with chronic obstructive pulmonary disease and obstructive sleep apnea. Tissue ischemia is believed to deplete ATP levels and activate the purine nucleotide degradation pathway to uric acid, resulting in urate overproduction in the heart, lungs, liver and skeletal muscle.[18]

Another factor which is said to influence the overproduction of uric acid is reduced renal output or perfusion and excretion of uric acid. There have been studies which have linked the elevated serum uric acid levels to cardiac index and renal blood perfusion. Our study also shows an inverse correlation between the cardiac index and uric acid levels which may suggest a lowered perfusion to the kidneys and thus elevated uric acid levels.[18,19]

Recent evidence suggests that uric acid inhibits acetylcholine-mediated vasodilation by acting on the vascular endothelium.[20] Treatment with Ibuprofen for three months have shown an improvement in the endothelial function in such patients.[21] A positive correlation in the NYHA class similar to our study was shown in a study involving 29 subjects with pulmonary arteria hypertension. Uric acid levels were higher in the patients who died.[22] A study by Nagaya et al involving 90 patients with primary pulmonary hypertension found that patients with high serum uric acid levels exhibited a significantly higher mortality rate compared with patients with low serum uric acid levels.[18]

CONCLUSION

In conclusion, the results of this study establish that hyperuricemia is common in patients with severe PH. There is also a strong correlation between the elevated uric acid levels and mortality among the patients and the NYHA class. We suggest that the uric acid levels can be a guide to predict the pulmonary hypertension thereby initiating timely treatment to the patient. Since the

numbers of patients was small in our study, more studies need to be conducted to ascertain these results.

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Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Van Albada ME, Loot FG, Fokkema R, Roofthooft MT, Berger RM. Biological Serum Markers in the Management of Pediatric Pulmonary Arterial Hypertension. Pediatric Research. 2008;63:321-7.
2. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. Metabolism.1981;30:616-34.
3. Leyva F, Anker S, Swan JW, Godsland IF, Wingrove CS, Chua TP, et al. Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure. Eur Heart J. 1997;18:858-65.
4. Hayabuchi Y, Matsuoka S, Akita H, Kuroda Y. Hyperuricemia in cyanotic congenital heart disease. Eur J Pediatr. 1999;152(11):873-6.
5. Hasday JD, Cyril M. Grun "nocturnal increase of urinary uric acid: creatinine ratio". American Review of Respiratory Disease. 1987;135(3):534-8.
6. Braghiroli A, Sacco C, Erbetta M, Ruga V, Claudio F. Donner"overnight urinary uric acid: creatinine ratio for detection of sleep hypoxemia: validation study in chronic obstructive pulmonary disease and obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure", American Rev Respir Dis. 1993;148(1):173-8.
7. Elsayed NM, Nakashima JM, Postlethwait EM. Measurement of uric acid as a marker of oxygen tension in the lung. Arch Biochem Biophys Arch Biochem Biophys. 1993;302(1):228-32.
8. Hughes JD, Rubin LJ. Primary pulmonary hypertension: an analysis of 28 cases and a review of the literature. Medicine (Baltimore). 1986;65(1):56-72.
9. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med. 1987;107(2):216-23.
10. Rich S. Primary pulmonary hypertension. Prog. Cardiovasc. 1988;31(3):205-38.
11. Higenbottam T, Stenmark K, Simonneau G. Treatments for severe pulmonary hypertension, Lancet. 1999;353:338-9.
12. Rubin LJ. Primary pulmonary hypertension. N Engl J Med. 1997;336:111-7.
13. Chun-Yan Z, Long-Le M, Le-Xin W. Relationship between serum uric acid levels and ventricular function in patients with idiopathic pulmonary hypertension. Exp Clin Cardiol. 2013;18(1):e37-9.
14. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115:343-9.
15. Chapman PJ, Bateman ED, Benatar SR. Prognostic and therapeutic considerations in clinical primary pulmonary hypertension. Respir Med. 1990;84:489-94.
16. Sandoval J, Bauerle O, Palomar A, Gomez A, Martinez-Guerra ML, Beltran M, Guerrero ML. Survival in primary pulmonary hypertension. Validation of a prognostic equation. Circulation. 1994;89:1733-44.
17. Voelkel MA, Wynne KM, Badesch DB, Groves BM, Voelkel NF. Hyperuricemia in Severe Pulmonary Hypertension. Chest. 2000;117(1):19-24.
18. Nagaya N, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Nakanishi N, et al. Serum uric acid levels correlate with the severity and the mortality of primary pulmonary hypertension. Am J Respir Crit Care Med. 1999;160:487-92.
19. Ross EA, Perloff JK, Danovitch GM, Child JS, Canobbio MM. Renal function and urate metabolism in late survivors with cyanotic congenital heart disease. Circulation. 1986;73:396-400.
20. Khosla UM1, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int. 2005;67:1739-42.
21. Mercuro G1, Vitale C, Cerquetani E, Zoncu S, Deidda M, Fini M, et al. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. Am J Cardiol. 2004;94:932-5.
22. Bendayan D, Shitrit D, Ygla M, Huerta M, Fink G, Kramer MR. Hyperuricemia as a prognostic factor in pulmonary arterial hypertension. Respir Med. 2003;97:130-3.

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